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(54) Title: SYNERGISTIC COMBINATION

(57) Abstract: The invention relates to the combined administration of PDE inhibitors and β_2 adrenoceptor agonists for the treatment of respiratory tract disorders.

Synergistic combination

Field of application of the invention

The invention relates to the combination of certain known active compounds for therapeutic purposes.

The substances used in the combination according to the invention are known active compounds from the PDE inhibitors class and active compounds from the β_2 adrenoceptor agonists class. Their combined use in the sense according to the invention for therapeutic purposes has not yet been described in the prior art.

Description of the invention

It is the object of the present invention to make available respiratory tract therapeutics which fulfill the following conditions:

- Good antiinflammatory action
- Marked bronchorelaxation and -dilatation
- Good oral availability, at least with respect to the PDE inhibitor
- Minor side effects
- Good suitability for long-term therapy
- Favorable influence on bronchial hyperreactivity.

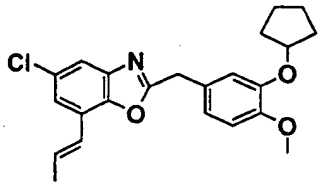
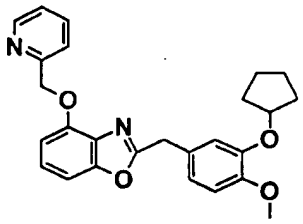
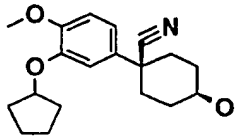
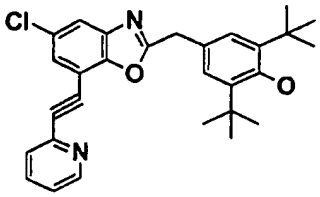
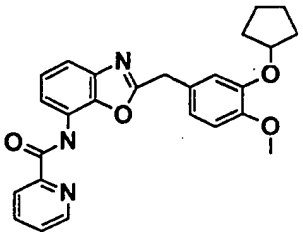
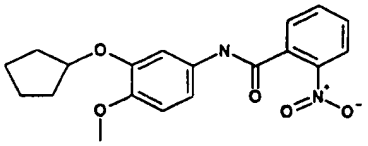
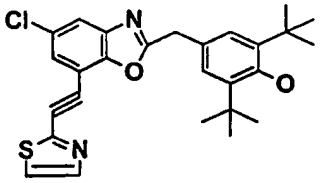
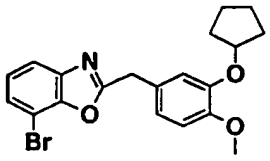
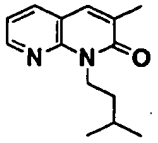
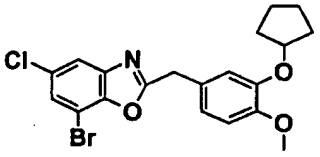
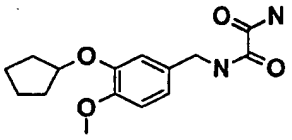
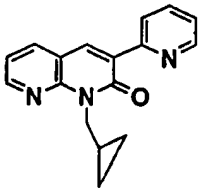
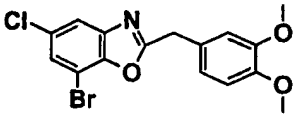
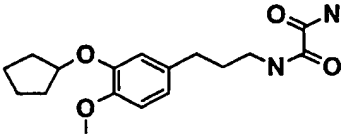
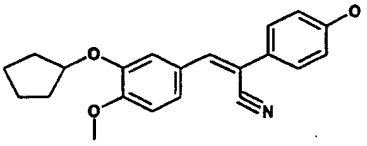
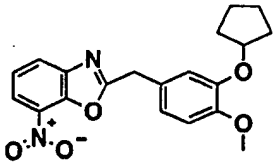
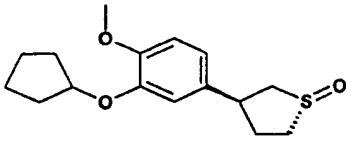
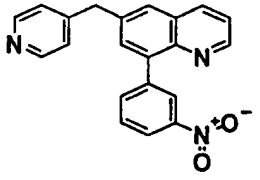
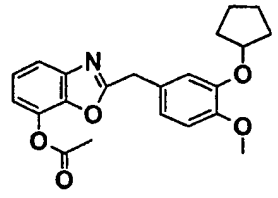
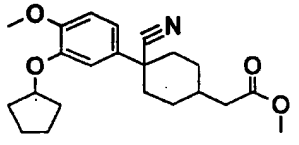
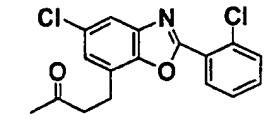
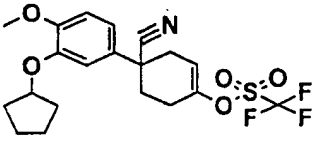
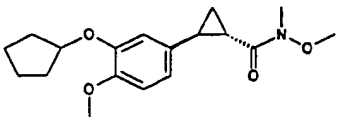
It has now been found that the combined use of a PDE inhibitor which can be used as a respiratory tract therapeutic and of a β_2 adrenoceptor agonist outstandingly fulfills the abovementioned conditions.

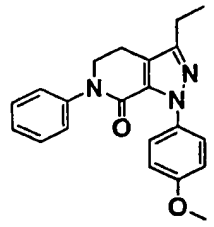
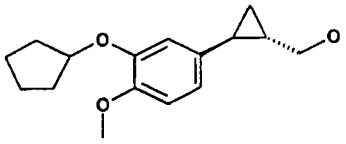
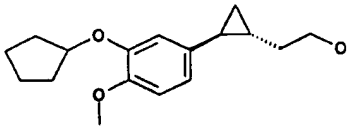
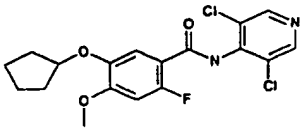
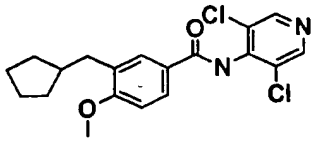
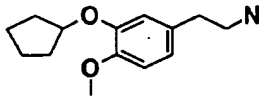
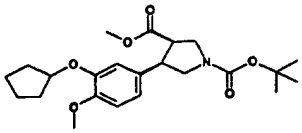
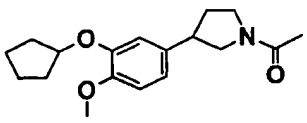
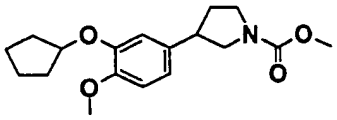
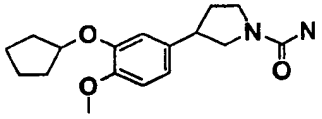
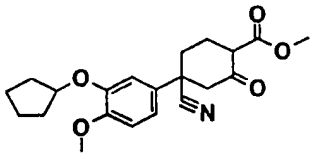
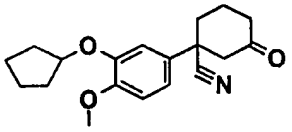
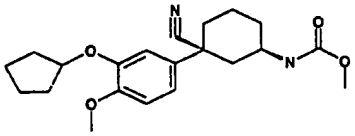
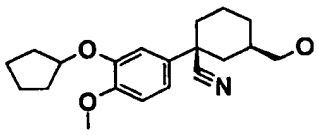
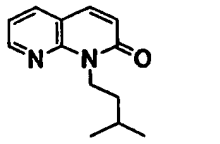
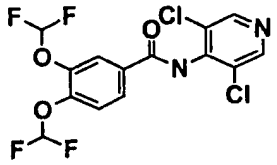
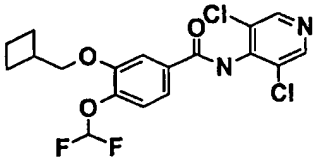
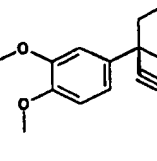
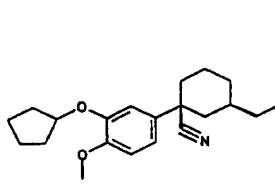
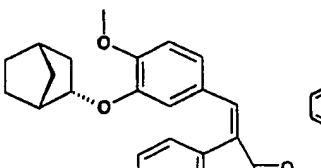
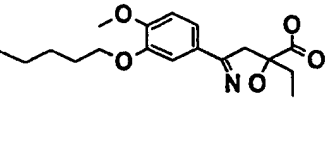
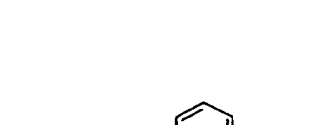
The invention thus relates to the combined use of a PDE inhibitor which can be used as a respiratory tract therapeutic and a β_2 adrenoceptor agonist in the treatment of respiratory tract disorders.

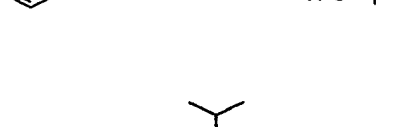
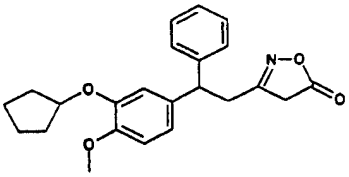
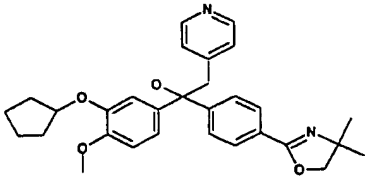
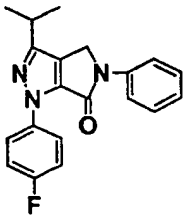
PDE inhibitors which can be used as respiratory tract therapeutics in the sense of the present invention are those compounds which slow the breakdown of cyclic AMP (cAMP) or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP or cGMP.

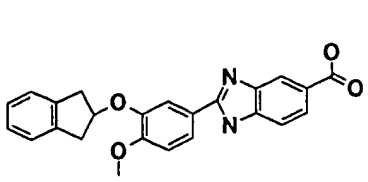
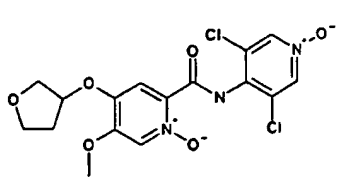
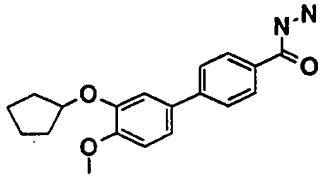
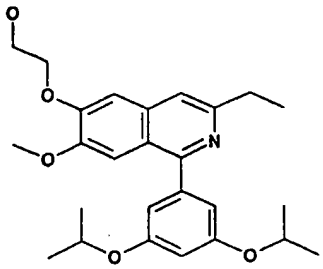
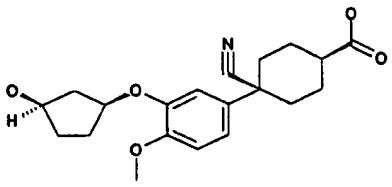
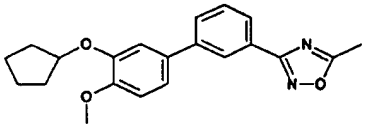
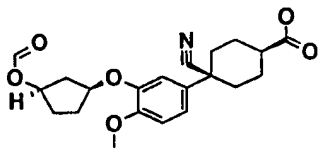
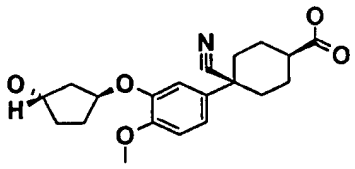
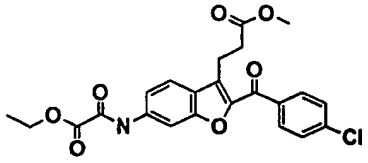
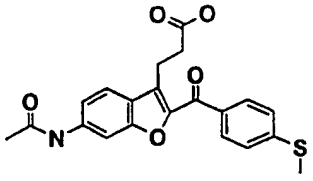
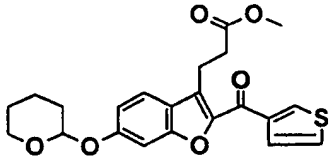
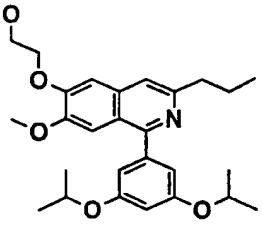
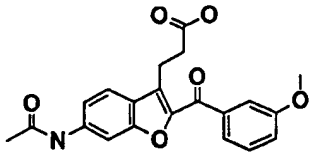
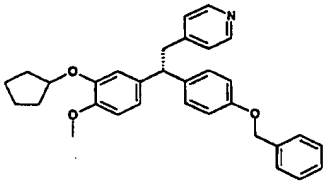
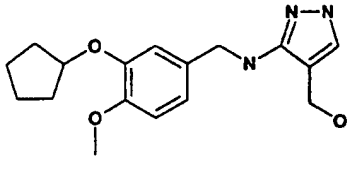
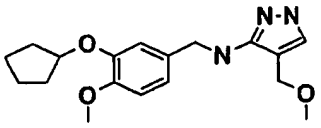
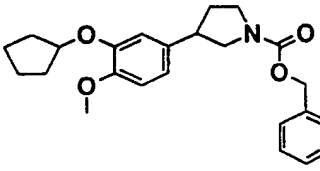
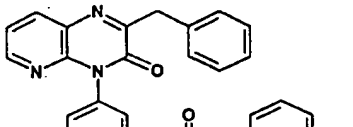
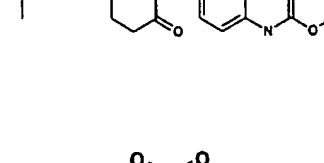
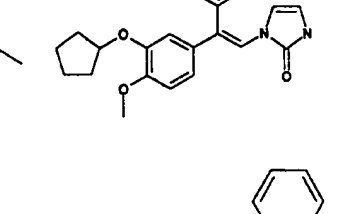
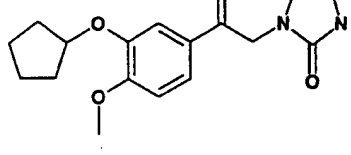
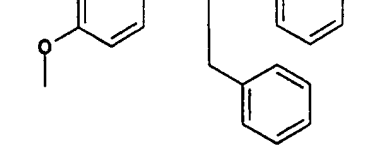
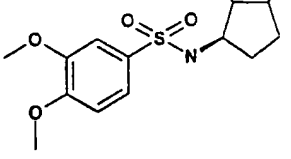
Possible PDE inhibitors within the meaning of the present invention are primarily those substances which are to be considered part of the PDE4 inhibitor class and those substances which can be designated as mixed types of PDE3/4 inhibitors. By way of example, those PDE inhibitors may be mentioned which are described or claimed in the following patent applications and patents: DE 1545687, DE 2028869, DE 2123328, DE 2315801, DE 2402908, DE 2413935, DE 3900233, EP 0103497, EP 0139464, EP 0158380, EP 0163965, EP 0335386, EP 0389282, EP 0428302, EP 0435811, EP 0459505, EP 0470805, EP 0490823, EP 0506194, EP 0511865, EP 0527117, EP 0557016, EP 0626939, EP 0664289, EP 0671389, EP 0685474, EP 0685475, EP 0685479, EP 0736532, EP 0738715, EP 0748805, EP 0763534, EP 0816357, EP 0819688, EP 0819689, EP 0832886, EP 0834508, EP 0848000, JP 92234389, JP 94329652, JP 95010875, JP 98072415, JP 98147585, US 5703098, US 5739144, WO 9117991, WO 9200968, WO 9212961, WO 9307146, WO 9315044, WO 9315045, WO 9318024, WO 9319068, WO 9319720, WO 9319747, WO 9319749, WO 9319751, WO 9325517, WO 9402465, WO 9412461, WO 9420455, WO 9422852, WO 9427947, WO 9501338, WO 9501980, WO 9503794, WO 9504045, WO 9504046, WO 9505386, WO 9508534, WO 9509623, WO 9509624, WO 9509627, WO 9509836, WO 9514667, WO 9514680, WO 9514681, WO 9517392, WO 9517399, WO 9519362, WO 9520578, WO 9522520, WO 9524381, WO 9527692, WO 9535281, WO 9535283, WO 9535284, WO 9600218, WO 9601825, WO 9606843, WO 9611690, WO 9611917, WO 9612720, WO 9631486, WO 9631487, WO 9635683, WO 9636595, WO 9636596, WO 9636611, WO 9636625, WO 9636638, WO 9638150, WO 9639408, WO 9640636, WO 9703967, WO 9704779, WO 9705105, WO 9708143, WO 9709345, WO 9712895, WO 9718208, WO 9719078, WO 9720833, WO 9722585, WO 9722586, WO 9723457, WO 9723460, WO 9723461, WO 9724117, WO 9724355, WO 9725312, WO 9728131, WO 9730999, WO 9731000, WO 9732853, WO 9735854, WO 9736905, WO 9743288, WO 9744036, WO 9744322, WO 9747604, WO 9748697, WO 9804534, WO 9805327, WO 9806692, WO 9806704, WO 9807715, WO 9808828, WO 9808830, WO 9808841, WO 9808844, WO 9809946, WO 9809961, WO 9811113, WO 9814448, WO 9818796, WO 9821208, WO 9822453, WO 9845268, WO 9855481, WO 9856756, WO 9905111, WO 9905112, WO 9505113, WO 9906404 and WO 9918095. Those PDE inhibitors are to be emphasized which are claimed in the patent applications or patents EP 0393500, EP 0510562, EP 0553174, WO 9501338, WO 9603399, WO 9636625, WO 9636626, WO 9735854, WO 9821208, WO 9831674, WO 9840382, WO 9855481, WO 9905111, WO 9905112, WO 9905113, WO 9931071 and WO 9931090. Substances having good oral availability are preferred here.

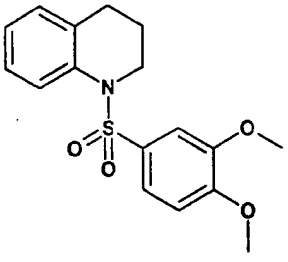
Exemplary PDE inhibitors are shown on the following pages with the aid of their formulae:

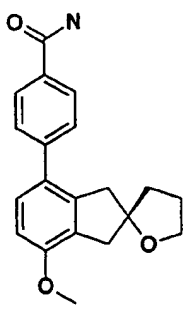
























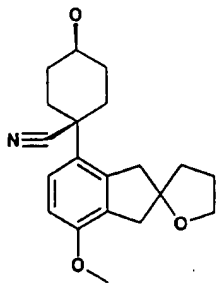























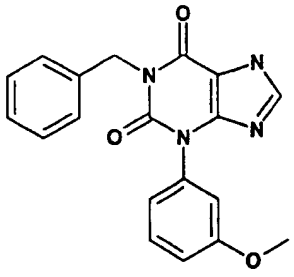





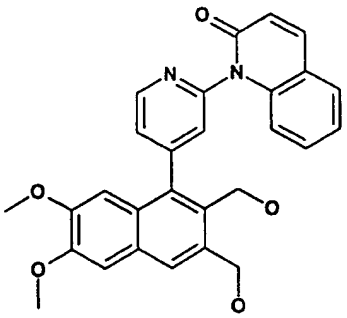
























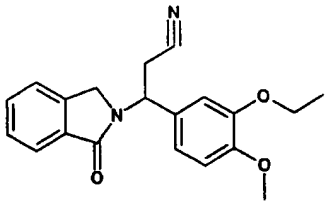


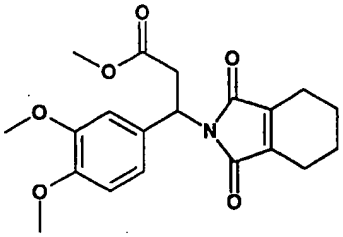


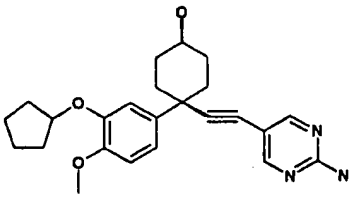


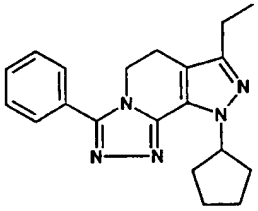


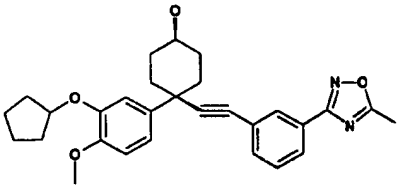


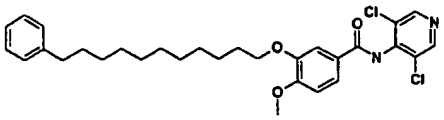


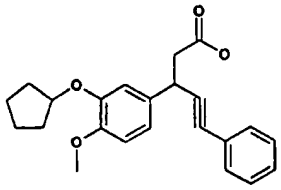


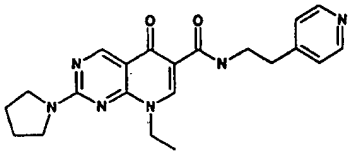


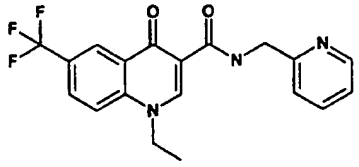


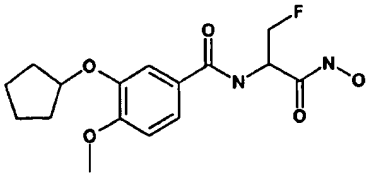


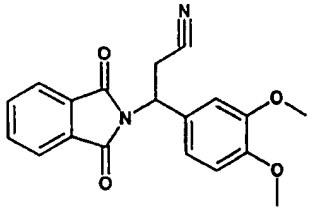


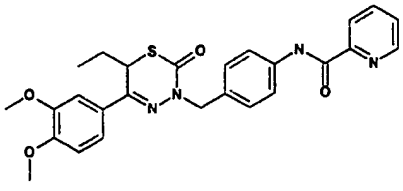


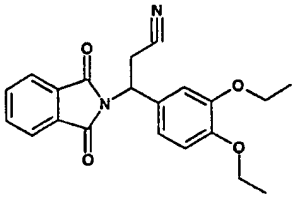


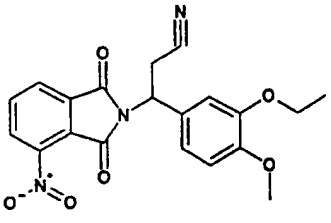


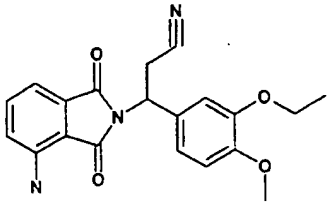


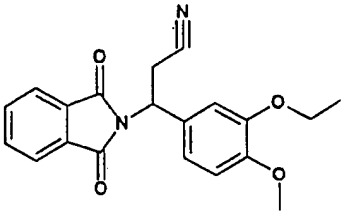


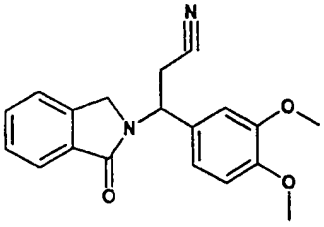


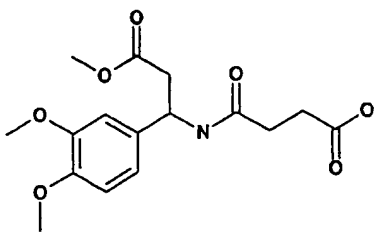
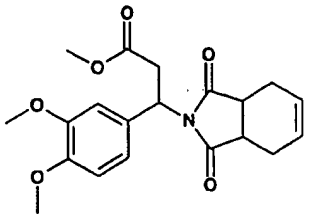
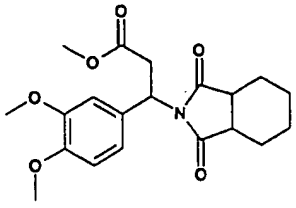
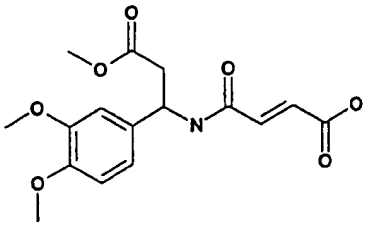
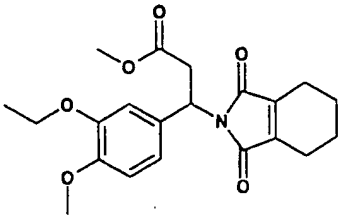
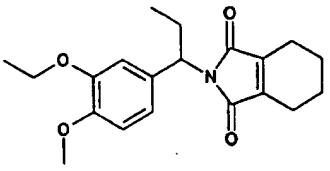
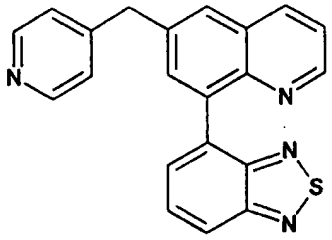
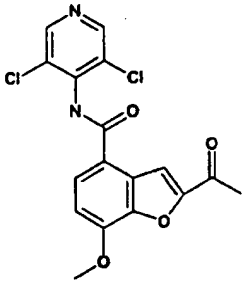
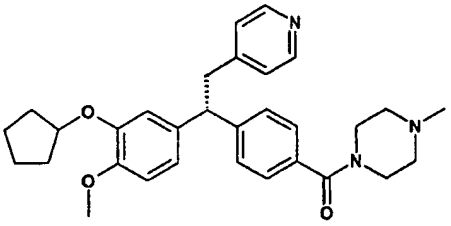
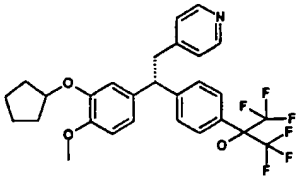
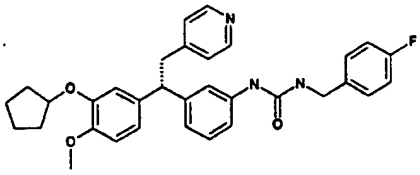
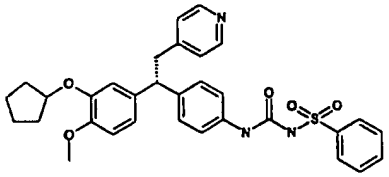
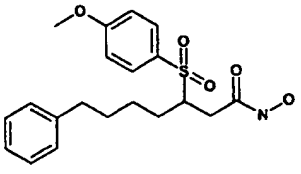
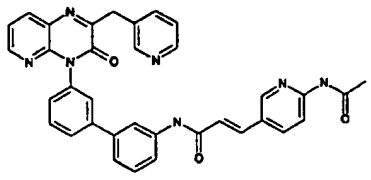
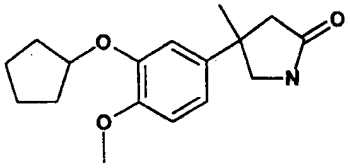
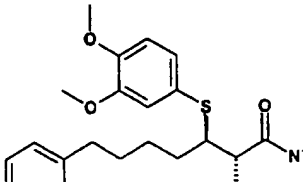
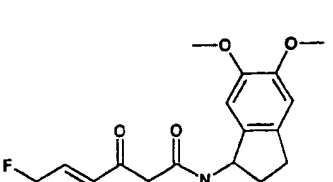
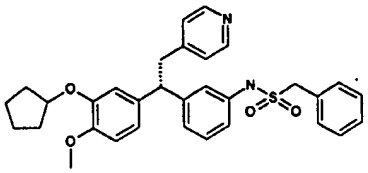
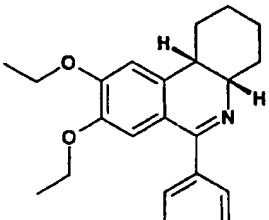
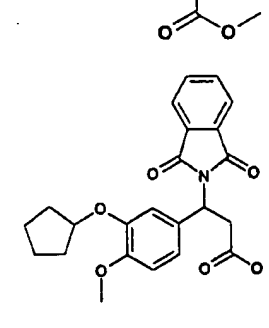


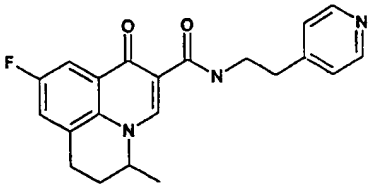


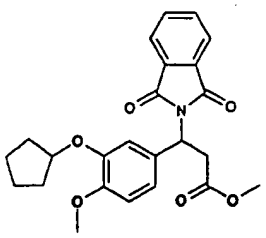
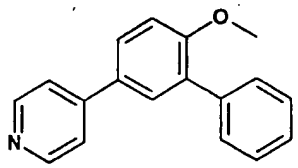
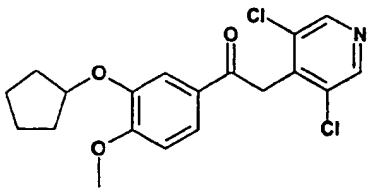
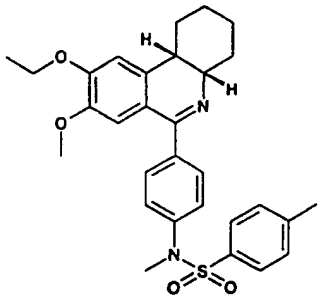
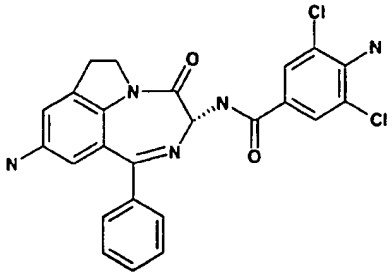
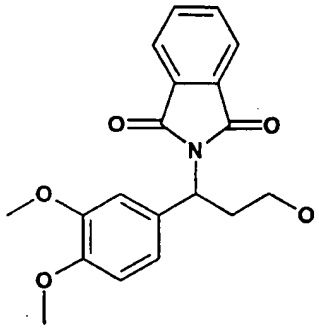
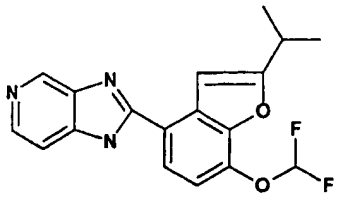
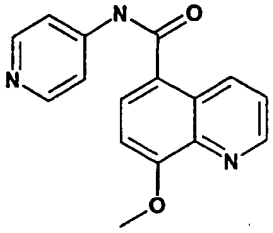
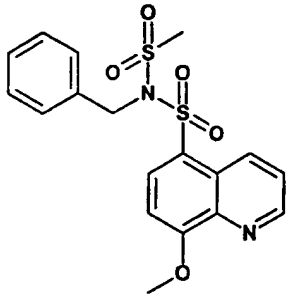
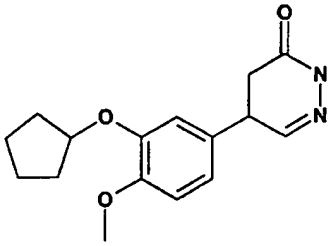
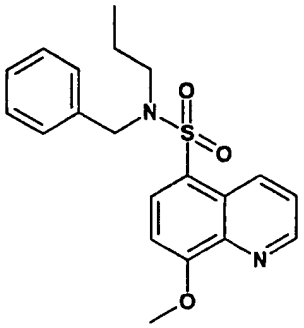
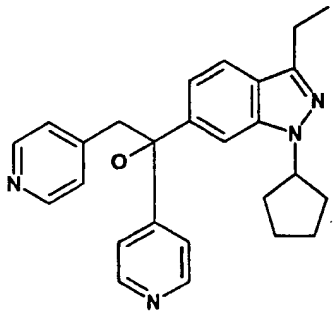
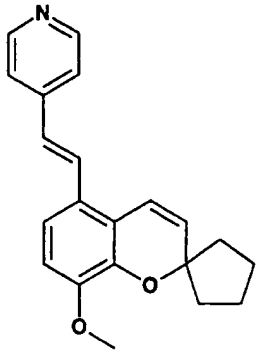
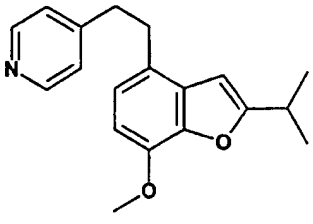


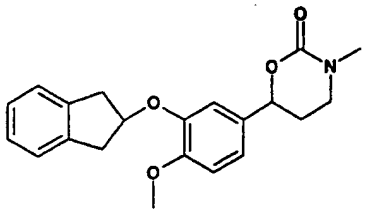
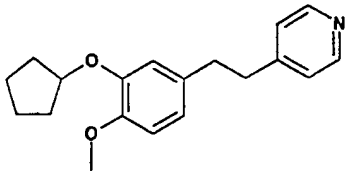
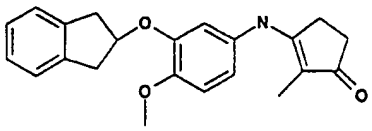
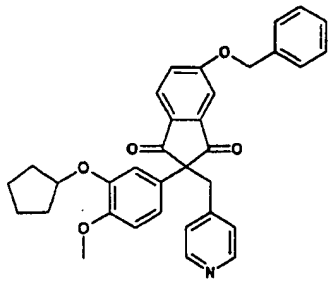


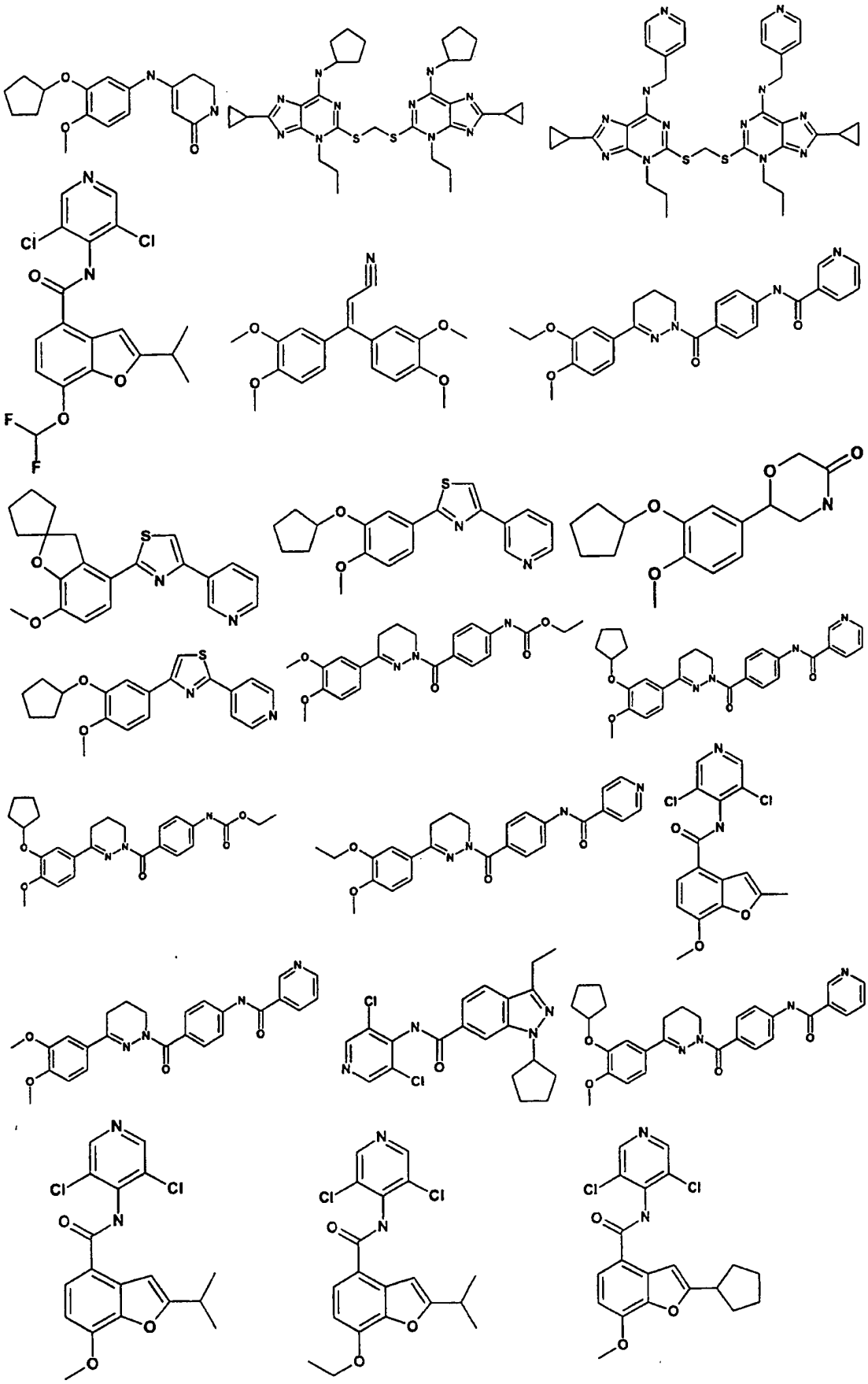


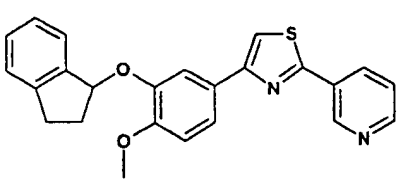
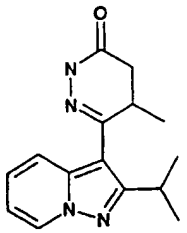
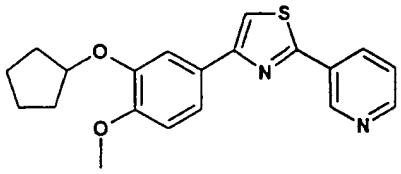
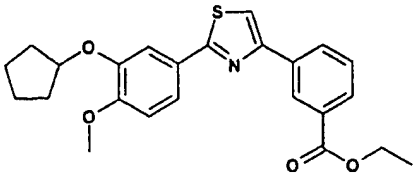
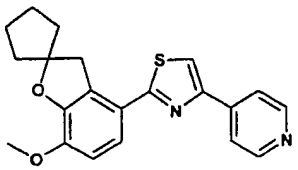
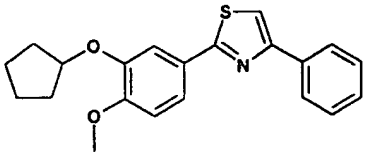
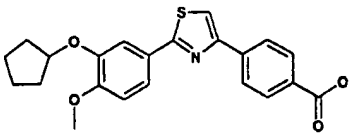
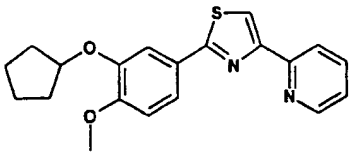
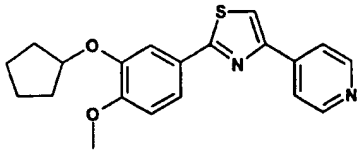
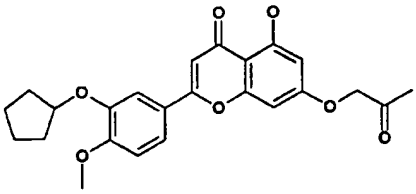
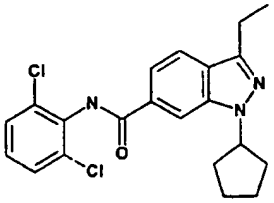
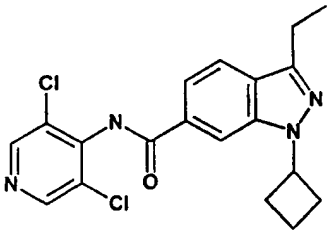
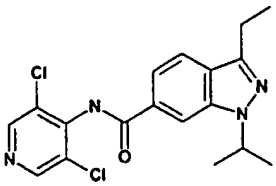
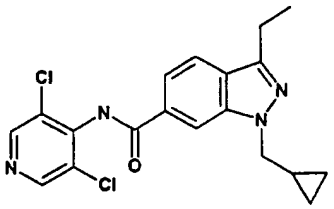
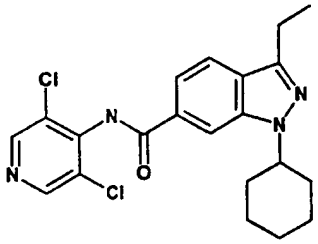
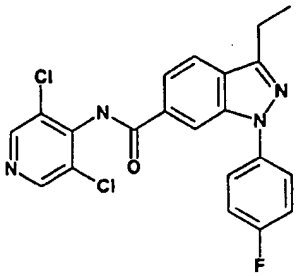
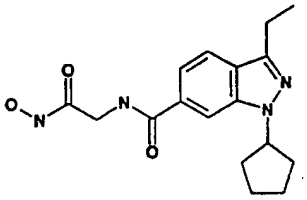
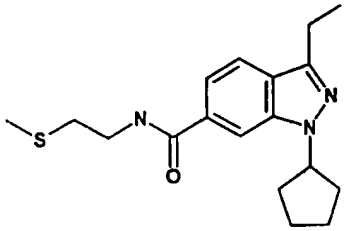
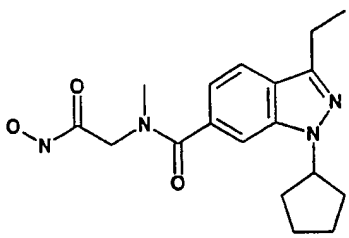
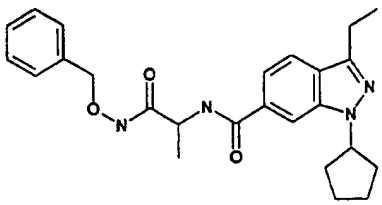
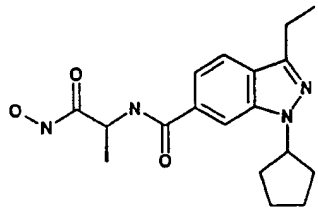





















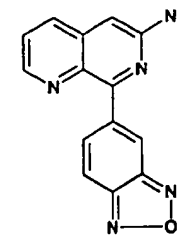
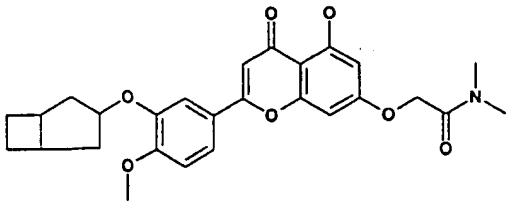
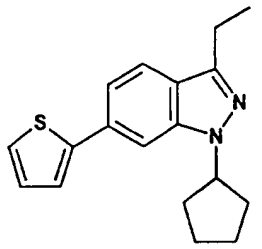
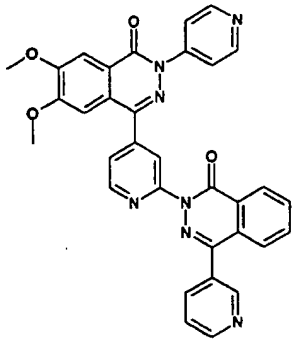
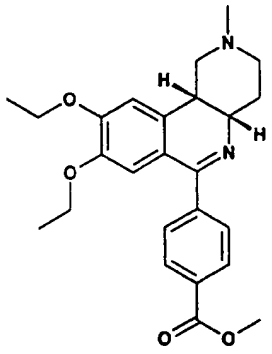
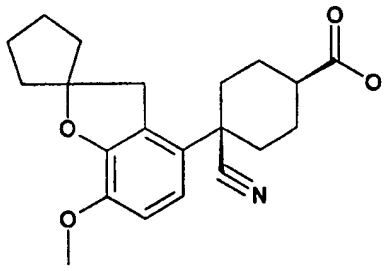
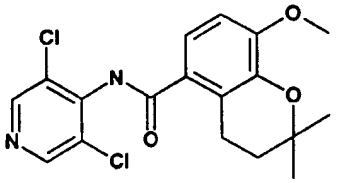
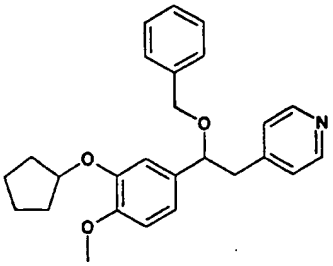
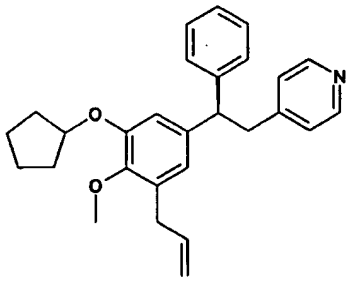
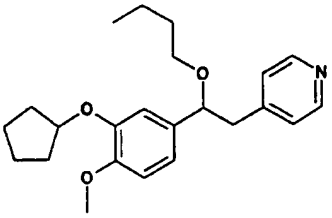
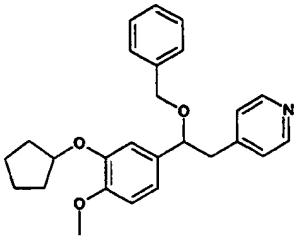
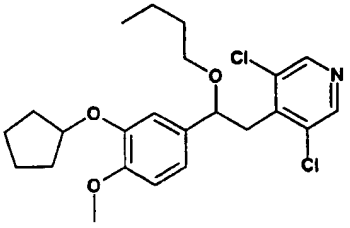
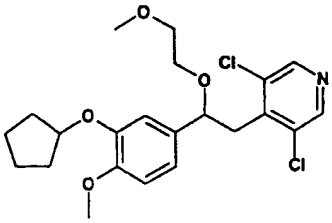
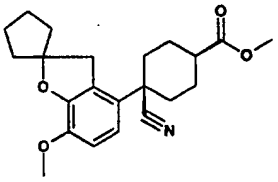
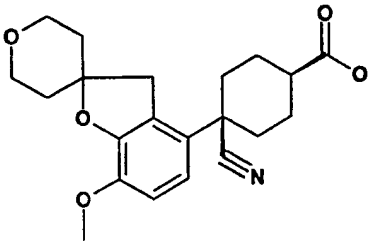
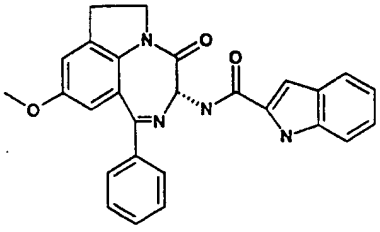
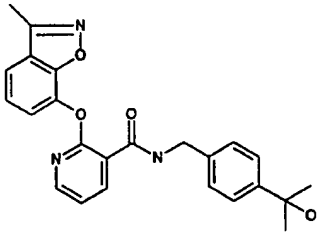
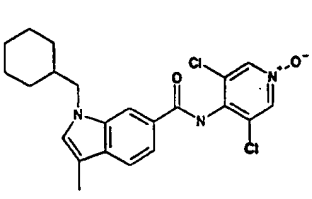


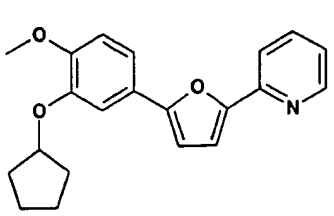
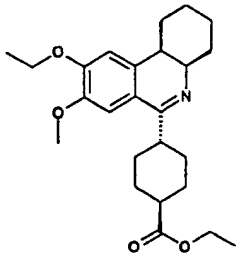
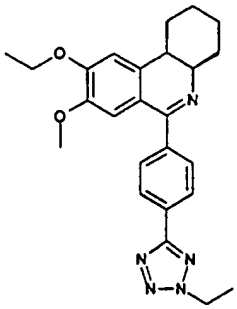
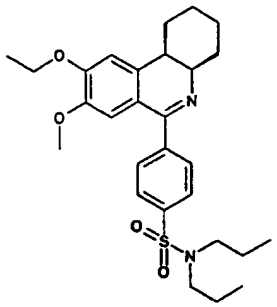
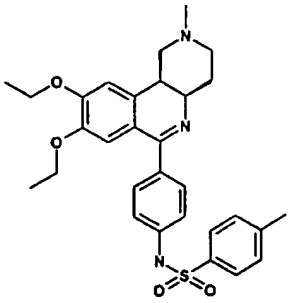
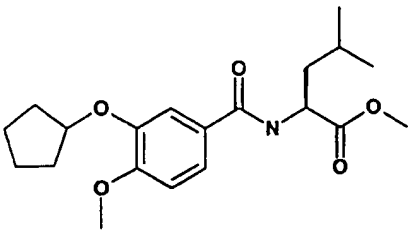
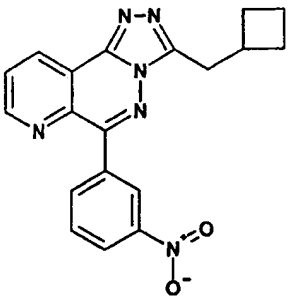
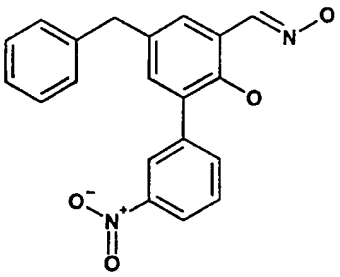
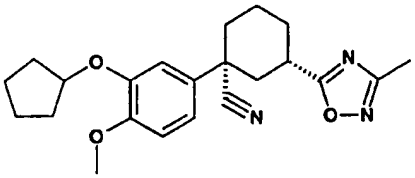
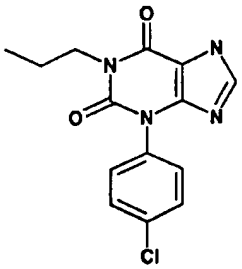
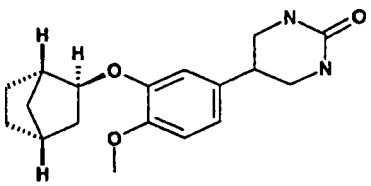
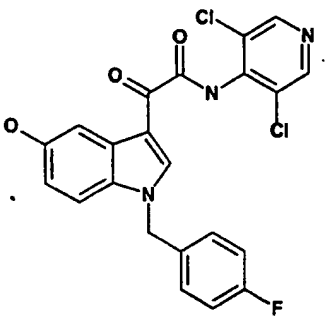
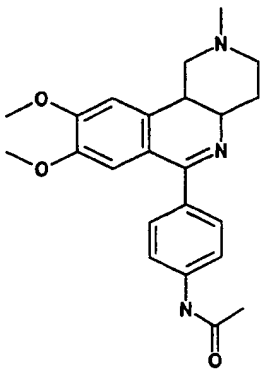
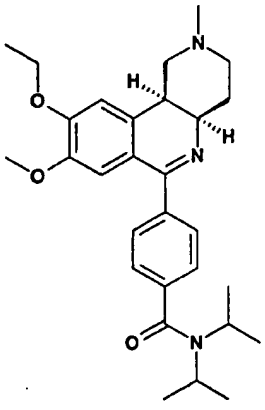
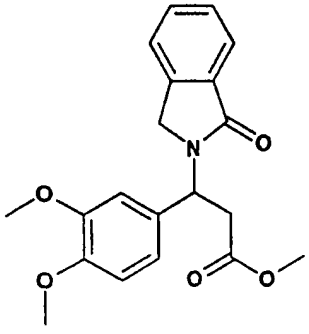















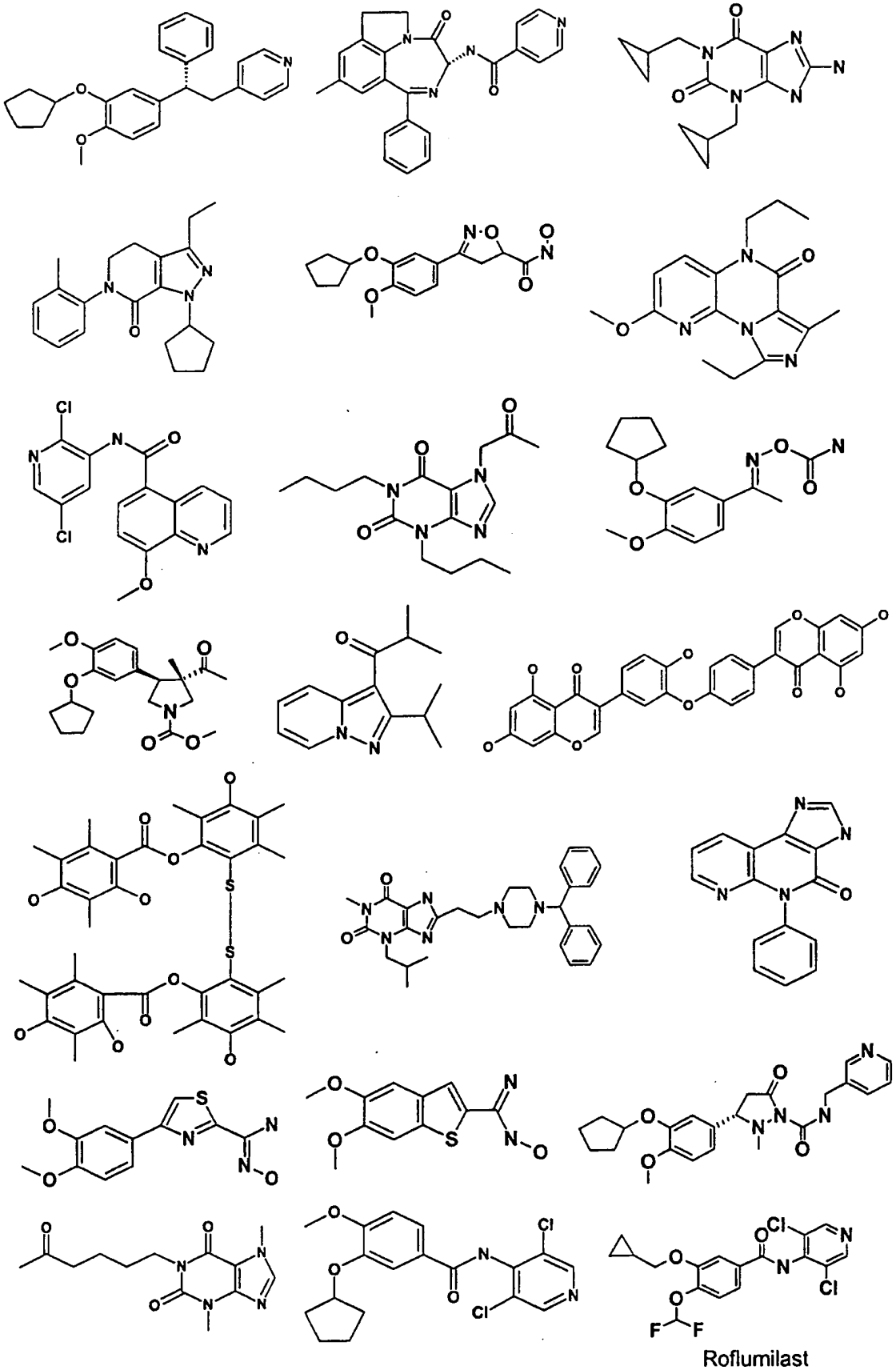


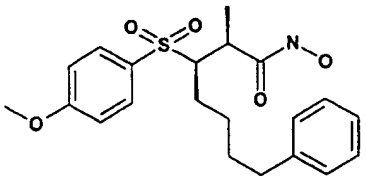
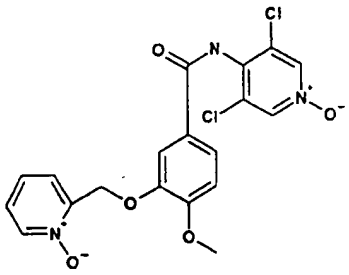
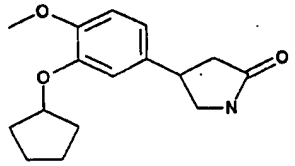



















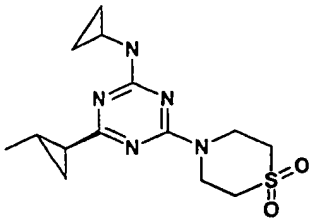
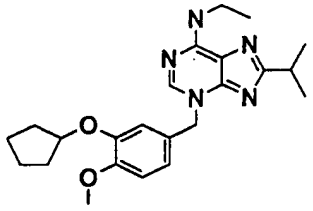
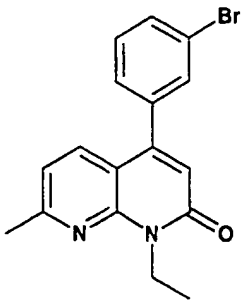
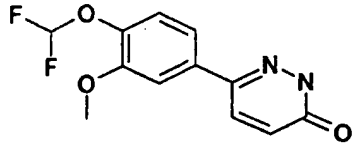
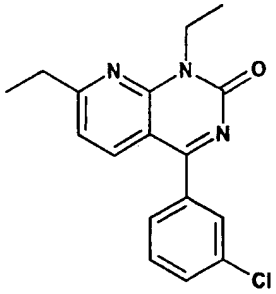
















BYK-33043
(Pumafentrin)



Roflumilast

No hydrogen atoms are indicated in the above formulae. -O is accordingly -OH, -N is NH_2. Methyl groups, e.g. on the oxygen atoms, are indicated by lines.

PDE inhibitors to be emphasized which are selected from the abovementioned compounds and which may be mentioned are the active compounds arofylline, atizoram, AWD-12-281, BAY-19-8004, benafentrine, BYK-33043, CC-3052, CDP-840, CI-1018, cipamfylline, CP-220629, CP-293121, D-22888, D-4396, D-4418, denbufylline, filaminast, GW-3600, ibudilast, KF-17625, KS-506-G, laprafylline, NA-0226A, NA-23063A, ORG-20241, ORG-30029, PDB-093, pentoxifylline, piclamilast, roflumilast, rolipram, RPR-117658, RPR-122818, RPR-132294, RPR-132703, RS-17597, RS-25344-000, SB-207499, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, SDZ-ISQ-844, SDZ-MNS-949, SKF-107806, SQ-20006, T-2585, T-440, tibenelast, tolafentrine, UCB-29646, V-11294A, YM-58997, YM-976 and zardaverine.

The compounds preferred from the group of the abovementioned PDE inhibitors are arofylline, cipamfylline, D-4418, filaminast, ibudilast, laprafylline, ORG-20241, piclamilast, rolipram, SB-207499, tibenelast and V-11294A. The compounds particularly preferred are BYK-33043 and in particular roflumilast.

β_2 adrenoceptor agonists which may particularly be mentioned are those selectively acting substances which only have a slight cardiac action and therefore are also employed in therapy, in particular in the oral therapy of respiratory tract disorders. β_2 adrenoceptor agonists which may be mentioned are, for example: AR-C68397AA, broxaterol, CHF-1035,

HOKU-81, ibuterol, KUL-1248, soterenol, meluadrine, TA-2005, tiaramide, salbutamol, levosalbutamol, tulobuterol, terbutaline, carbuterol, pirbuterol, reproterol, clenbuterol, fenoterol, hexoprenaline, orciprenaline, isoprenaline, formoterol, salmeterol, rimiterol, procaterol, bambuterol, bitolterol and mabuterol. The orally readily available β_2 adrenoceptor agonists such as clenbuterol, orciprenaline, salbutamol, terbutaline, tulobuterol, bambuterol and reproterol are preferred. Particularly preferred are the so-called long acting β_2 adrenoceptor agonists, such as salmeterol.

The PDE inhibitors and the β_2 adrenoceptor agonists can be present as such or in chemically bonded form. It is understood hereby that the active compounds mentioned can also be present, for example, in the form of their pharmacologically tolerable salts and/or as solvates (e.g. hydrates), and/or in the form of their N-oxides etc. Suitable pharmacologically tolerable salts here are in particular water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)-benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 1-hydroxy-2-naphthoic acid, the acids being employed in salt preparation – depending on whether it is a mono- or polybasic acid and depending on which salt is desired – in an equimolar quantitative ratio or one differing therefrom. Furthermore, the active compounds mentioned can also be present as pure enantiomers or as enantiomer mixtures in any mixing ratio.

Respiratory tract disorders which may be mentioned are in particular allergen- and inflammation-induced bronchial disorders (bronchitis, obstructive bronchitis, spastic bronchitis, allergic bronchitis, allergic asthma, bronchial asthma, COPD), which can be treated by the combination according to the invention also in the sense of a long-term therapy (if desired with appropriate adjustment of the dose of the individual components to the needs at the time, for example needs subject to seasonally related variations).

"Combined use" or "combination" within the meaning of the present invention is to be understood as meaning that the individual components can be administered simultaneously (in the form of a combination medicament), more or less simultaneously (from separate pack units) or in succession (directly in succession or else alternatively at a relatively large time interval) in a manner which is known per se and customary.

Within the meaning of the present invention, "use" is preferably understood as meaning the oral administration of both active compounds. If only the PDE inhibitor is administered orally, "use" with respect to the β_2 adrenoceptor agonist is understood in particular as meaning

topical application in inhalatory form. For this, the β_2 adrenoceptor agonist is preferably administered by inhalation in the form of an aerosol, the aerosol particles of solid, liquid or mixed composition having a diameter of 0.5 to 10 µm, advantageously of 2 to 6 µm.

Aerosol generation can be carried out, for example, by pressure-driven jet atomizers or ultrasonic atomizers, but advantageously by propellant-driven metered aerosols or propellant-free administration of micronized active compounds from inhalation capsules.

The active compounds are dosed in an order of magnitude customary for the individual dose, it more likely being possible, on account of the individual actions, which are mutually positively influencing and reinforcing, to reduce the respective doses on the combined administration of the active compounds compared with the norm. Customarily, the β_2 adrenoceptor agonist (depending on potency) is administered in a dose of, for example, 0.002 to 2.0 mg per day on administration by inhalation.
Depending on the inhaler system used, in addition to the active compounds the administration forms additionally contain the required excipients, such as, for example, propellants (e.g. Frigen in the case of metered aerosols), surface-active substances, emulsifiers, stabilizers, preservatives, flavorings, fillers (e.g. lactose in the case of powder inhalers) or, if appropriate, further active compounds.

For the purposes of inhalation, a large number of apparatuses are available with which aerosols of optimum particle size can be generated and administered, using an inhalation technique which is as right as possible for the patient. In addition to the use of adaptors (spacers, expanders) and pear-shaped containers (e.g. Nebulator®, Volumatic®), and automatic devices emitting a puffer spray (Autohaler®), for metered aerosols, in particular in the case of powder inhalers, a number of technical solutions are available (e.g. Diskhaler®, Rotadisk®, Turbohaler® or the inhaler described in European Patent Application EP 0 505 321), using which an optimal administration of active compound can be achieved.

In the case of the oral administration of the β_2 adrenoceptor agonists together with the PDE inhibitor, which is the preferred administration form, the β_2 adrenoceptor agonist is administered in a daily dose of, for example, 0.05 to 60 mg. For the PDE inhibitors, it is possible in the case of oral administration to vary the doses – depending on the active compound – within a wide range, it being possible, as bounds, to start from a dose of 1 - 2000 µg/kg of body weight. In the case of the administration of the preferred PDE inhibitor roflumilast, the dose is in the range from 2 - 20 µg/kg of body weight.

The PDE inhibitors to be administered orally are formulated – if appropriate together with the β_2 adrenoceptor agonists – to give medicaments according to processes known per se and

familiar to the person skilled in the art. The pharmacologically active compounds are employed as medicaments, preferably in combination with suitable pharmaceutical excipients or vehicles, in the form of tablets, coated tablets, capsules, emulsions, suspensions or solutions, the active compound content advantageously being between 0.1 and 95% and, by the appropriate choice of the excipients and vehicles, it being possible to achieve a pharmaceutical administration form precisely tailored to the active compound(s) and/or to the desired onset of action (e.g. a sustained-release form or an enteric form). Particularly worthy of mention within the meaning of the combined, oral administration of both active compounds according to the invention are oral administration forms, e.g. tablets or capsules, in which one part of the β_2 adrenoceptor agonist and the PDE inhibitor is present in non sustained-release form and a further, preferably larger part, of the β_2 adrenoceptor agonist is present in sustained-release form.

The person skilled in the art is familiar on the basis of his/her expert knowledge with which excipients or vehicles are suitable for the desired pharmaceutical formulations. In addition to solvents, gel-forming agents, tablet excipients and other active compound carriers, it is possible to use, for example, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers, colorants or permeation promoters and complexing agents (e.g. cyclodextrins).

Pharmacology

Model

Late Inflammatory Airway Reaction in the Ovalbumin-sensitized/-challenged Brown-Norway Rat

Anti-inflammatory activity of Roflumilast, Pumafentrine (BYK-33043), and Salmeterol was determined in ovalbumin (OVA)-sensitized and OVA-challenged Brown Norway rats. Sensitization was done by simultaneous injection of Bordetella pertussis suspension i.p. and OVA/AHG suspension s.c. on day 1, 14 and 21. 28 days after start of sensitization, conscious Brown-Norway rats were challenged by inhalation of the aerosolized OVA solution for 1 h (~20 ml/h). Non-challenged, only sensitized animals were used as baseline control. The drugs (thoroughly mixed with lactose) or the placebo control (lactose) were administered intratracheally (i.t.) as dry powders 1 h before OVA-challenge. 48h later, OVA-challenged or non-challenged animals were anaesthetized and bronchoalveolar lavage (BAL) was performed using 3x4 ml BAL buffer per animal. The number of total cells and eosinophils in the BAL fluid, and the concentration of protein in the cell-free BAL fluid were determined. Drug-induced relative changes were calculated and statistically analyzed by the Jonckheere Terpstra test.

Results

Compound	PDE3/4 IC50[µmol]	Dose [µmol/kg]	Appl. Route	N	% Inhibition of Infiltration/Accumulation [Median / Mean ± SEM]		
					Total cells	EOS	Protein
Roflumilast	>10/0.0007	0.3	it	8	-25	-15	-8
					-37.6±26.7	-22±25.7	-22.3±25.5
Pumafentrine	0.028/0.007	3	it	8	-19	-26	17
					-39.1±30.5	-28.5±30.1	23.5±10.6
Salmeterol		3	it	8	19	39	44
					6.3±17.9	31±14.8	37.5±16.2
Salmeterol/ Roflumilast		3/0.3	it	8	50	67 **	59 **
					34.5±21.1	61.1±7.9 **	50.8±13.6 **
Salmeterol/ Pumafentrine		3/3	it	8	56 *	85 **	75 **
					58.1±12.3 *	83±3.7 **	67.1±11.1 **

***p< 0.05, ** p< 0.01 v.s. untreated, OVA-challenged control groups**

Summary

The PDE inhibitors Roflumilast (PDE4 inhibitor) and Pumafentrine (PDE3>4 inhibitor) administered at doses of 0.3 µmol/kg and 3 µmol/kg i.t., respectively, did not show any significant effects on cell infiltration and protein accumulation. The negative values obtained (trend: amplification of inflammation) fall into the range of biological variability of the model and therefore, no significance must be attached to these data.

In contrast, the long-acting β2-adrenergic receptor agonist Salmeterol given at a dose of 3 µmol/kg i.t exhibited inhibitory effects on total cell and eosinophil influx into alveolar space and protein levels in BAL fluid. However, the data failed to reach significance.

Co-administration of the PDE inhibitor Roflumilast or Pumafentrine with Salmeterol resulted in synergistic effects compared to administration of every compound alone, i.e. both PDE inhibitors combined with the β2 agonist displayed a significant inhibition of eosinophilia and reduction of protein concentration in the BAL fluid. The combination of the PDE3/4 inhibitor Pumafentrine and Salmeterol was more efficacious on all parameters measured (difference was not significant), and additionally, showed a significant effect on inhibition of total cell influx into the alveolar space.

Patent claims

1. A medicament comprising a PDE inhibitor, which is to be administered orally, from the PDE4 or PDE3/4 inhibitors group combined with a β_2 adrenoceptor agonist in fixed or free combination.

2. The medicament as claimed in claim 1, which is a fixed oral combination.

3. The medicament as claimed in claim 1 or 2 for use in the therapeutic treatment of respiratory tract disorders.

4. The medicament as claimed in claim 1 or 2, wherein the PDE inhibitor is a compound selected from the group consisting of arofylline, cipamfylline, D-4418, filaminast, ibudilast, laprafylline, ORG-20241, piclamilast, rolipram, SB-207499, tibenelast and V-11294A or a salt thereof.

5. The medicament as claimed in claim 1 or 2, wherein the PDE inhibitor is roflumilast, its salt and/or its N-oxide.

6. The medicament as claimed in claim 1 or 2, wherein the PDE inhibitor is BYK-33043, its salt and/or its N-oxide.

7. The medicament as claimed in claim 1 or 2, wherein the PDE inhibitor is roflumilast, its salt and/or its N-oxide and the β_2 adrenoceptor agonist is salmeterol or a salt thereof.

8. The medicament as claimed in claim 1 or 2, wherein the PDE inhibitor is BYK-33043, its salt and/or its N-oxide and the β_2 adrenoceptor agonist is salmeterol or a salt thereof.

9. The medicament as claimed in claim 1 or 2, wherein the β_2 adrenoceptor agonist is clenbuterol, orciprenaline, salbutamol, terbutaline, tulobuterol, bambuterol or reproterol or a salt thereof.

10. The medicament as claimed in claim 1 or 2, wherein the PDE inhibitor is arofylline, cipamfylline, D-4418, filaminast, ibudilast, laprafylline, ORG-20241, piclamilast, rolipram, SB-207499, tibenelast or V-11294A or a salt thereof, and the β_2 adrenoceptor agonist is clenbuterol, orciprenaline, salbutamol, terbutaline, tulobuterol, bambuterol or reproterol or a salt thereof.

11. The medicament as claimed in claim 1 or 2, wherein the PDE inhibitor is roflumilast or BYK-33043, their salts and/or their N-oxides and the β_2 adrenoceptor agonist is clenbuterol, orciprenaline, salbutamol, terbutaline, tulobuterol, bambuterol or reproterol or a salt thereof.

12. The use of a PDE inhibitor, which is to be administered orally, from the PDE4- or PDE3/4 inhibitors group in the combined use with a β_2 adrenoceptor agonist in the therapeutic treatment of respiratory tract disorders.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: SYNERGISTIC COMBINATION OF PDE INHIBITORS AND BETA 2 ADRENOCEPTOR AGONIST

(57) Abstract: The invention relates to the combined administration of PDE inhibitors and β_2 adrenoceptor agonists for the treatment of respiratory tract disorders.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K45/06 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, AIDSLINE, BIOSIS, CHEM ABS Data, CANCERLIT, EMBASE, MEDLINE, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 840 537 A (GARSIDE S ET AL) 8 October 1974 (1974-10-08) abstract column 2, line 63 -column 3, line 5	1-3,9,12
X	FR 2 390 164 A (BLANIE PAUL) 8 December 1978 (1978-12-08) page 1, line 1-21	1-3,9,12
X	US 5 602 110 A (DRUMM MITCHELL L ET AL) 11 February 1997 (1997-02-11) column 3, line 44 - line 54 claims 1-3	1-3,9,12
X	US 3 941 785 A (CLARKE ROBERT WILLIAM ET AL) 2 March 1976 (1976-03-02) column 3, line 13 - line 21 column 1, line 14 - line 25	1-3,9,12

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2001	28/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Leherte, C

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INTERNATIONAL SEARCH REPORT

Int. ational Application No
PCT/EP 00/07852

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	RAEBURN, DAVID (1) ET AL: "Anti-inflammatory and bronchodilator properties of RP 73401, a novel and selective phosphodiesterase type IV inhibitor." BRITISH JOURNAL OF PHARMACOLOGY, (1994) VOL. 113, NO. 4, PP. 1423-1431., XP000889938 page 1428, column 1, paragraph 2 ---	1,3,4,9, 10,12
X	BLEASE, KATE ET AL: "Modulation of cell adhesion molecule expression and function on human lun microvascular endothelial cells by inhibition of phosphodiesterases 3 and 4." BRITISH JOURNAL OF PHARMACOLOGY, (MAY, 1998) VOL. 124, NO. 1, PP. 229-237, XP000890110 page 232, column 2, paragraph 4 page 231; figure 2 ---	1,3,4,9, 10,12
X	DENT, GORDON ET AL: "Suppression of Human Eosinophil Respiratory Burst and Cyclic AMP Hydrolysis by Inhibitors of Type IV Phosphodiesterase: Interaction with the Beta Adrenoceptor Agonist Albuterol." JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, (1994) VOL. 271, NO. 3, PP. 1167-1174., XP000889916 page 1170, column 1, paragraph 3 -page 1171, column 2, paragraph 1 ---	1,3,4,9, 10,12
X	PLANQUOIS, JM ET AL: "Salbutamol potentiates the relaxant effects of selective phosphodiesteras inhibitors on guinea pig isolated trachea" FUNDAM. CLIN. PHARMACOL. (1996), 10(4), 356-367, 1996, XP000889917 page 360, column 1, paragraph 4 -column 2, paragraph 1; figure 2 -----	1,3,4,9, 10,12

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-6, 9, 12

Present claims 1-6, 9 and 12 relate to a compounds defined (inter alia) by reference to the following parameters: " PDE4 or PDE 3/4-inhibitors" and " beta 2-adrenoceptor agonist".
The use of these parameters in the present context is considered to lead to a lack of clarity within the meaning of Article 6 PCT. It is impossible to compare the parameters the applicant has chosen to employ with what is set out in the prior art. The lack of clarity is such as to render a meaningful complete search impossible. Consequently, the search has been restricted to the combinations of claims 7, 8, 10 and 11, with due regard to the therapeutic application mentioned in claim 3 and 12.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/EP 00/07852

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
US 3840537 A	08-10-1974	GB	1400999 A	16-07-1975
		AT	321923 B	25-04-1975
		AU	472127 B	20-05-1976
		AU	4819172 A	16-05-1974
		BE	791025 A	07-05-1973
		CA	990292 A	01-06-1976
		CH	594671 A	13-01-1978
		DE	2255172 A	24-05-1973
		DK	138691 B	16-10-1978
		ES	408736 A	01-03-1976
		FR	2160407 A	29-06-1973
		IE	37046 B	27-04-1977
		IL	40686 A	31-12-1975
		JP	1059812 C	25-08-1981
		JP	48057993 A	14-08-1973
		JP	56003873 B	27-01-1981
		NL	7215646 A	22-05-1973
		PH	9669 A	10-02-1976
		SE	402915 B	24-07-1978
		ZA	7207532 A	25-07-1973
FR 2390164 A	08-12-1978	NONE		
US 5602110 A	11-02-1997	AU	3541595 A	22-03-1996
		WO	9606612 A	07-03-1996
US 3941785 A	02-03-1976	GB	1457873 A	08-12-1976
		AT	336029 B	12-04-1977
		AT	2374 A	15-08-1976
		AU	474078 B	15-07-1976
		AU	6377473 A	19-06-1975
		BE	809369 A	03-07-1974
		CA	1005057 A	08-02-1977
		CH	618170 A	15-07-1980
		DE	2364076 A	18-07-1974
		ES	422001 A	01-08-1976
		FI	57260 B	31-03-1980
		FI	793137 A	10-10-1979
		FR	2213058 A	02-08-1974
		IE	38681 B	10-05-1978
		IL	43872 A	31-01-1979
		JP	49095994 A	11-09-1974
		LU	69099 A	02-04-1974
		NL	7400095 A	08-07-1974
		NO	140301 B	30-04-1979
		SE	408179 B	21-05-1979
		ZA	7309534 A	27-11-1974